

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COMPLETE GENOMICS, INC.,
Petitioner,

v.

ILLUMINA CAMBRIDGE LTD.,
Patent Owner.

Case IPR2017-02174
Patent 7,566,537 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

ILLUMINA EX. 1095 ILLUMINA V. COLUMBIA IPR2018-00291, -00318, -00322, -00385, and -00797

I. INTRODUCTION

Complete Genomics, Inc. (“CGI” or “Petitioner”), on October 5, 2017, filed a Petition to institute *inter partes* review of claims 1–6 and 8 of U.S. Patent No. 7,566,537 B2 (“the ’537 patent”). Paper 1 (“Pet.”).¹ Illumina Cambridge Ltd. (“Patent Owner”), on January 23, 2018, filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”).

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless the Petition “shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” For the reasons stated below, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–6 and 8 of the ’537 patent.

II. BACKGROUND

A. *Related Matters*

Petitioner identifies other proceedings related to the ’537 patent. Pet. 4–7. The identified proceedings include, *inter alia*, the following:

- 1) IPR2013-00517 (petition for *inter partes* review by Intelligent Bio-Systems, Inc. (“IBS”));
- 2) IPR2013-00518 (petition for *inter partes* review by IBS);
- 3) *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016) (appeal of IPR2013-00517);
- 4) *Illumina, Inc. v. Qiagen, N.V.*, 207 F.Supp.3d 1081 (N.D.

¹ Petitioner identifies BGI Shenzhen Co., Ltd. (and other BGI companies) as a real party-in-interest to these proceedings. Pet. 4.

Cal. 2016) (involving assertion of the '537 patent against Qiagen and its subsidiary, IBS);

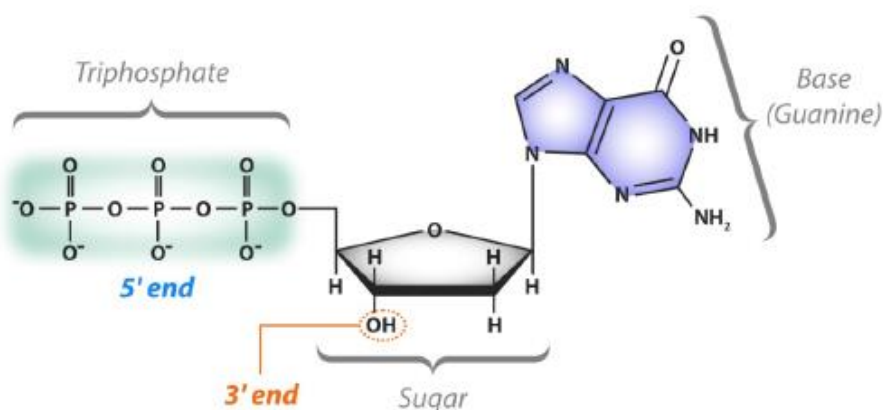
- 5) *The Trustees of Columbia University v. Illumina, Inc.*, 1:12-cv-00376-GMS (D. Del.) (involving assertion of patents against Illumina, and assertion of the '537 patent against IBS, Columbia's licensee of the accused technology); and
- 6) IPR2017-02172 (petition for *inter partes* review by CGI, filed concurrent with the present Petition).

Pet. 4–7. We describe these proceedings in more detail in Section II.E. below.

B. Background Technology and the '537 Patent

The '537 patent relates generally to labeled nucleotides and nucleosides, and to methods of using such molecules in, for example, nucleic acid sequencing reactions. Ex. 1501, 2:1–7.

A “nucleotide” consists of a nitrogenous base, a sugar, and one or more phosphate groups. *Id.* at 4:48–49. An illustrative depiction of a deoxyribonucleotide triphosphate is provided below.



Ex. 1601, ¶ 8. The depiction above shows, *inter alia*, the 3'-hydroxyl (3'-OH) group of the deoxyribose sugar; the sugar of a DNA nucleotide is a 2'

deoxyribose, meaning the 2' carbon lacks a bond to an oxygen atom. *Id.*

¶ 10 (depicting 2-deoxyribose and ribose); Ex. 1501, 4:49–51 (“In RNA, the sugar is a ribose, and in DNA is a deoxyribose, i.e., a sugar lacking a hydroxyl group that is present in ribose [at the 2' carbon]”).

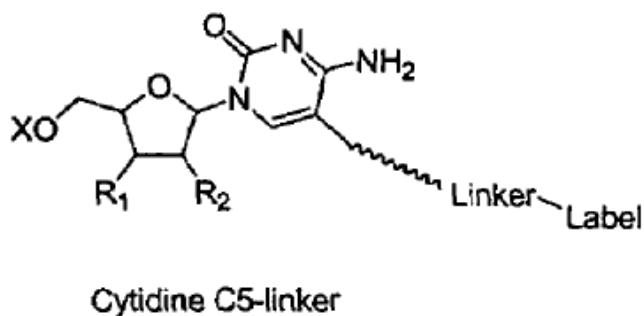
Nucleotides, such as depicted above, are building blocks of DNA and, through complementary base-pairing, form molecules of DNA that consist of two associated nucleic acid strands and a double-helical structure that resembles a twisting ladder. Ex. 1601, ¶¶ 8–9. Natural DNA contains four bases: the base may include a purine or pyrimidine, such as the purines adenosine (A) and guanine (G), and the pyrimidines cytosine (C) and thymine (T). Ex. 1501, 4:51–54. The sequence of these bases in DNA provides genetic information, and ultimately encodes the traits in living organisms. *Intelligent Bio-Systems*, 821 F.3d at 1362.

A base of one DNA strand bonds with the complementary base on the opposing strand in a known pattern: A pairs with T, and G pairs with C. Ex. 1601, ¶ 9. Because of this pattern of base pairing, if the sequence of one strand is known, the other strand's sequence can be deduced. *Id.* In addition, enzymes (e.g., DNA polymerase) may cause the strand to be extended with the phosphate group on the 5' carbon of each additional nucleotide attaching to the 3'-OH of the last nucleotide in the strand via a new phosphodiester bond. *Id.* ¶ 11. The added nucleotide is one that, as explained above, bonds with its complementary base of the nucleotide at a corresponding position on the opposing nucleic acid strand. *Id.* ¶ 9; Ex. 1501, 2:50–53.

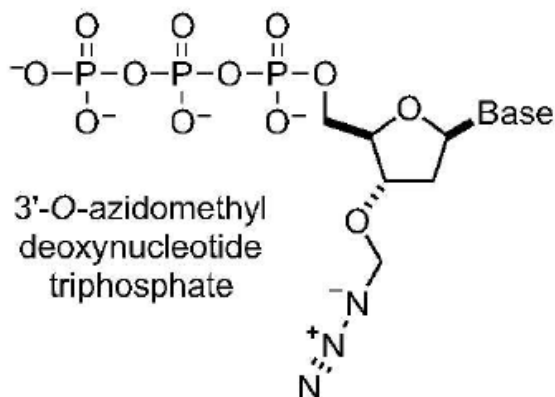
As described in the '537 patent, “[t]he invention features a nucleotide or nucleoside molecule, having a base that is linked to a detectable label via a cleavable linker.” Ex. 1501, 2:23–24. The label may be, for example, a

fluorophore that is detectable by fluorescence spectroscopy. *Id.* at 5:20–25. The nucleotide also includes a ribose or deoxyribose sugar, which “sugar can include a protecting group attached via the 2' or 3' oxygen atom,” and the protecting group “can be removed to expose a 3'-OH.” *Id.* at 2:25–28.

The '537 patent depicts several exemplary labeled nucleotide structures, such as shown below.



Ex. 1501, Fig. 1 (partial). Figure 1 (partial) above shows a nucleotide having a base (here cytidine) attached to a label via a linker. *Id.* The '537 patent explains that “X” in this molecule can be, for example, a triphosphate, and that R_1 and R_2 may be selected from H, OH, or any group that can be transformed into an OH. *Id.* at 4:7–11. Among the “suitable hydroxyl protecting groups” that can be transformed into an OH, the '537 patent identifies azidomethyl (CH_2N_3). *Id.* at Fig. 3. A further representation of an azidomethyl protecting group is shown below.



Ex. 1601, ¶ 143. The representation above shows a 3'-O-azidomethyl deoxynucleotide triphosphate, where the azidomethyl group is attached to the 3' oxygen atom of the deoxyribose sugar moiety thereby protecting a nascent 3'-OH.

The '537 patent describes methods of labeling nucleic acids, in which an enzyme is used to incorporate a labeled nucleotide into the nucleic acid molecule. Ex. 1501, 2:32–38. The '537 patent also describes methods of using labeled and blocked nucleotides to determine the sequence of a target single-stranded polynucleotide. *Id.* at 2:50–57. More specifically, the '537 patent explains that this method

can be carried out by contacting the target polynucleotide separately with the different nucleotides to form the complement to that of the target polynucleotide, and detecting the incorporation of the nucleotides. Such a method makes use of polymerisation, whereby a polymerase enzyme extends the complementary strand by incorporating the correct nucleotide complementary to that on the target. The polymerisation reaction also requires a specific primer to initiate polymerisation.

Id. at 8:50–58. Because the 3'-OH of the nucleotide(s) to be added is protected by a protecting group, the enzyme incorporates only one nucleotide at a time into the complementary strand, thus providing a controlled sequencing reaction. *Id.* at 7:51–54. The detectable label uniquely identifies the particular type of nucleotide (e.g., containing a base “G”) that was incorporated into the growing complementary strand. *Id.* at 2:55–57, 5:20–24, 10:4–9. The label and protecting group are then removed, thus exposing a 3'-OH on the previously added nucleotide, and the process repeats with the addition of the next labeled and blocked nucleotide(s). *Id.* at 2:55–3:16, 7:43–8:14. By detecting, one-by-one, the type of nucleotides

that are added to the complementary strand, the sequence of the entire target polynucleotide chain can be determined. *Id.* at 2:50–3:3.

C. Illustrative Claims

Petitioner challenges claims 1–6 and 8. Claim 1, the only challenged independent claim, and dependent claim 6 are reproduced below:

1. A method of labeling a nucleic acid molecule, the method comprising incorporating into the nucleic acid molecule a nucleotide or nucleoside molecule, wherein the nucleotide or nucleoside molecule has a base that is linked to a detectable label via a cleavable linker and the nucleotide or nucleoside molecule has a ribose or deoxyribose sugar moiety, wherein the ribose or deoxyribose sugar moiety comprises a protecting group attached via the 2' or 3' oxygen atom, and said protecting group can be modified or removed to expose a 3' OH and the protecting group comprises an azido group.

6. The method according to claim 1, wherein the protecting group is CH₂N₃ [*i.e.*, azidomethyl].

Ex. 1501, 19:48–59, 20:3–4.

D. The Asserted Grounds of Unpatentability

Petitioner contends claims 1–6 and 8 are unpatentable under 35 U.S.C. § 103 based on the following grounds. Pet. 8–9.

Ground	References	Basis	Claims
1	Dower, ² Church, ³ and Zavgorodny ⁴	§ 103	1, 2, 4–6, and 8

² Dower et al., US 5,547,839, issued Aug. 20, 1996. Ex. 1504.

³ Church et al., WO 00/53812 A2, published Sept. 14, 2000. Ex. 1606.

⁴ Sergey Zavgorodny et al., *1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications: A New Versatile Method in Nucleoside Chemistry*, 32 TETRAHEDRON LETTERS 7593–96 (1991). Ex. 1508.

2	Dower, Church, Zavgorodny, and Prober ⁵	§ 103	3
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Petitioner also relies on the Declaration of John D. Sutherland, D. Phil. (Ex. 1601), and several ancillary references.

E. History of the '537 Patent at the U.S. Patent Office and in Other Legal Proceedings

i) Relevant Prosecution History

The '537 patent issued on July 28, 2009 from U.S. Application No. 11/301,578, filed December 13, 2005. Ex. 1501.⁶ Claim 9 (which later issued as claim 1) did not recite a “protecting group” or a “protecting group [that] comprises an azido group” when that claim was originally filed. Ex. 1502, 71. On October 30, 2007, the Examiner entered a rejection of claim 9 as anticipated by Ju.⁷ *Id.* at 84. On February 1, 2008, the applicants amended claim 9, adding a limitation of a “protecting group [that] comprises an azido group.” *Id.* at 71 (underlining omitted). The applicants also added, *inter alia*, new claim 34, which was substantially the same as claim 9 except that it recited “the protecting group comprises an allyl moiety.” *Id.* at 72. The applicants responded to the Examiner’s rejection, explaining the addition of the azido group to claim 9, and argued the amended and newly presented claims were not taught or suggested by the prior art. *Id.* at 77–78.

⁵ James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336–41 (1987). Ex. 1507.

⁶ This application is a divisional of US Application No. 10/227,131, filed on August 23, 2002 and which issued as US 7,057,026 B2 on June 6, 2006.

⁷ Ju et al., US 6,664,079 B2, issued Dec. 16, 2003. Ex. 1538.

The Examiner responded on May 16, 2008 with a rejection of claim 34 as obvious over Tsien and Greene & Wuts.⁸ *Id.* at 64. The Examiner determined that the 3'-OH allyl protecting group was implicitly disclosed in Tsien and also obvious in view of Greene & Wuts and “the Patent Owner’s admission that all of the protecting groups are known in the prior art.” *Id.* at 65. As to claim 9 (reciting an azido protecting group) and dependent claim 28 (reciting an azidomethyl (CH₂N₃) protecting group), the Examiner, without further comment, noted those claims were allowed. *Id.* On August 21, 2008, the applicants canceled claim 34 and its dependent claims, and requested allowance of the other pending claims. *Id.* at 59. Claims 9 and 28 later issued in the ’537 patent as claims 1 and 6, respectively. *Id.* at 25.

Dower, Church, and Zavgorodny appear in the references cited portion of the ’537 patent. Ex. 1501, 2 (left and right columns) and 3 (right column). The Examiner did not, however, specifically rely on these references or apply them to support a rejection during prosecution. Prober is referenced in the ’537 patent’s specification. Ex. 1501, 5:30–31.

ii) Prior Petitions for *Inter Partes* Review

In IPR2013-00518, IBS challenged claims 7 and 11–14 of the ’537 patent, which claims were canceled based on Patent Owner’s disclaimer and request for adverse judgment. Pet. 6; Exs. 1588 and 1589.

⁸ The Examiner appears to have relied on a prior edition of Greene & Wuts (Theodora W. Greene & Peter G.M. Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS (John Wiley & Sons, Inc., 1991) to the third edition relied upon in IPR2017-02172 and in IPR2013-00517. Ex. 1502, 64, 67.

In IPR2013-00517, IBS challenged claims 1–6 and 8 of the '537 patent on multiple obviousness grounds. Pet. 6; Ex. 1590, 6–7 (Rev. Petition dated Aug. 3, 2013, Paper 7). The specific grounds are below:

Ground	References	Basis	Claims
1a	Ju and Zavgorodny	§ 103	1–6 and 8
1b	Ju and Greene & Wuts ⁹	§ 103	1–6 and 8
1c	Tsien ¹⁰ and Zavgorodny	§ 103	1–6 and 8
1d	Tsien and Greene & Wuts	§ 103	1–6 and 8
2a	Tsien, Zavgorodny, and Prober	§ 103	3
2b	Tsien, Greene & Wuts, and Prober	§ 103	3

Ex. 1590, 7–8.

Patent Owner waived the filing of a preliminary response and, on February 13, 2014, the Board instituted *inter partes* review on claims 1–6 and 8 over Tsien (or Ju) in combination with Zavgorodny (grounds 1a and 1c in the table above). Ex. 1591, 2, 15. The Board further instituted review of claim 3 based on the combination of Tsien, Zavgorodny, and Prober (ground 2a). *Id.* The Board concluded the other grounds were redundant. *Id.* at 5, 15. On May 5, 2014, Illumina filed its Patent Owner Response. Ex. 1592. And, on July 28, 2014, IBS filed its Reply. Ex. 1593.

⁹ Theodora W. Greene & Peter G.M. Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 1–5, 14–23, 246–60 (John Wiley & Sons, Inc., 3rd ed. 1999). Ex. 1505.

¹⁰ Tsien, WO 91/06678 A1, published May 16, 1991. Ex. 1503.

The Board held a full trial and issued a Final Written Decision dated February 11, 2015. Ex. 1594. The Board determined the preponderance of the evidence did not support a conclusion that claims 1–6 and 8 were unpatentable. *Id.* at 3–4. Among other things, the Board “agree[d] with Patent Owner that Petitioner [had] not shown . . . that an ordinary artisan would have considered it obvious to use Zavgorodny’s azidomethyl group as the 3’ hydroxyl protecting group in Tsien’s processes.” *Id.* at 9. The Board further found that “the prior art suggests that an ordinary artisan would not have expected Zavgorodny’s azidomethyl group to be removed quantitatively, as Tsien requires.” *Id.* at 14. As explained by the Board, Tsien’s requirement for quantitative deblocking “mean[s] essentially 100% removal of the protecting group.” *Id.* at 12.

In reaching its conclusion, the Board also relied on Greene & Wuts and Loubinoux,¹¹ which together disclose removal of an azidomethyl protecting group from phenols (as distinct from simple aliphatic alcohols like the 3’ hydroxyl of a deoxyribonucleotide). *Id.* at 13. Based on the reported yields (60–80%) of deprotected phenols in Loubinoux, and Greene & Wuts’ teaching that a phenol is a better leaving group (i.e., is more easily cleaved) than a simple alcohol, the Board found that the ordinary artisan would have expected *inefficient* removal/deblocking of an azidomethyl moiety in Tsien’s methods. *Id.* at 13–14. Thus, the Board determined the ordinarily skilled person would not have been motivated to use an

¹¹ Bernard Loubinoux et al., *PROTECTION OF PHENOLS BY THE AZIDOMETHYLENE GROUP APPLICATION TO THE SYNTHESIS OF UNSTABLE PHENOLS*, 44 TETRAHEDRON 6055–64 (1988) (as translated). Ex. 1506. Greene & Wuts cites Loubinoux for the use of an azidomethyl group to protect phenols. Ex. 1505, 260.

azidomethyl group to meet Tsien’s sequencing criteria — especially the requirement for quantitative deblocking. *Id.* at 7, 18.¹²

iii) Proceedings Before the Federal Circuit

On May 9, 2016, the Federal Circuit affirmed the Board’s determination in IPR2013-00517 that claims 1–6 and 8 had not been shown to be obvious. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016). The court analyzed the prior art combination of Tsien and Zavgorodny. *Id.* at 1363–64. And, like the Board, the court accepted that Tsien required quantitative deblocking for successful use of 3’ blocking groups in Tsien’s DNA sequencing methods and that, “for the deblocking (i.e., the removal of the protecting group) to be quantitative, it must take place at 100% or near-100% efficiency.” *Id.* at 1364.

According to the Federal Circuit, although the challenged claims of the ’537 patent do not require quantitative deblocking, the expectation (or lack thereof) of high efficiency deblocking “is central to a finding of no motivation to combine.” *Id.* at 1368. That is so, the court explained, because the petitioner argued the skilled artisan would have been motivated to use Zavgorodny’s azidomethyl group with Tsien’s SBS (sequencing-by-synthesis) method to meet Tsien’s criteria. *Id.*¹³ Analyzing *Greene & Wuts* and *Loubinoux*, the court further concluded there was “substantial evidence

¹² The Board reached a similar conclusion with respect to the challenge based on *Ju* and *Zavgorodny*. Ex. 1594, 18–22.

¹³ As noted by the Federal Circuit, “IBS argued that an ordinary artisan, to improve the efficiency, reliability, and robustness of the sequencing by synthesis method taught by Tsien, would have been motivated to use other protecting groups that meet the criteria of Tsien, such as the azidomethyl group taught by *Zavgorodny*.” *Intelligent Bio-Systems*, 821 F.3d at 1364 (internal quotation marks and citation omitted); see also Ex. 1594, 7.

to support a finding that a person of ordinary skill would not have had a reason to combine Tsien or Ju with Zavgorodny to achieve the claimed invention.” *Id.* at 1368–69 (“These references [Greene & Wuts and Loubinoux] support a conclusion that the claimed efficiency that allegedly motivated the combination would not be achieved.”). Indeed, as the court held, “[t]his is so because the azidomethyl group would have been expected to perform inefficiently in that role [as a protecting group that can be removed to expose a 3'-OH group of a nucleotide].” *Id.* at 1369.

iv) Proceedings Before the District Courts

After the Federal Circuit’s decision, Patent Owner sued Qiagen N.V. and several of its subsidiaries (including IBS) in the Northern District of California, alleging infringement of the ’537 patent. *Illumina*, 207 F.Supp.3d at 1083, 1086. Patent Owner also moved for a preliminary injunction against Qiagen. *Id.* Qiagen did not deny that its accused DNA sequencing products were covered by claims 1–6 and 8 of the ’537 patent, and instead argued the claims would have been obvious over Tsien, Ju, and Greene & Wuts. *Id.* at 1087–88.

In its decision and order dated September 9, 2016, the district court found “Qiagen’s obviousness argument [was] unpersuasive” and “weak,” and held that Patent Owner “has shown it is *likely* to defeat Qiagen’s invalidity arguments.” *Id.* at 1088–90. The court determined, among other things, that “Greene & Wuts is an extensive treatise covering thousands of protecting groups for various purposes,” and that, while “Greene & Wuts does teach the use of azidomethyl . . . [,] that reference is in a chapter directed at phenols, which are hydroxyl groups [] of a different type than the hydroxyl group that appears in nucleotides or nucleosides.” *Id.* at 1098.

Also, the court found, “Greene & Wuts offers an entirely separate chapter on aliphatic alcohols, which include the types of hydroxyl groups that appear in nucleotides and nucleosides . . . [but] makes no mention of azido groups” in that chapter. *Id.* The court pointed to testimony from Qiagen’s expert admitting that the removal conditions for azidomethyl disclosed in Greene & Wuts would be inappropriate for use with nucleotides and would alter DNA structures. *Id.* And, the court cited to the earlier decisions by the Board and Federal Circuit related to IPR2013-00517 and their analysis of Tsien and Greene & Wuts. *Id.* at 1090 n.2. In so doing, the court agreed that Greene & Wuts “would have indicated a low likelihood of success in using azidomethyl in the process taught by Tsien.” *Id.* at 1090. The court ultimately granted the preliminary injunction. *Id.* at 1093–94. According to Patent Owner, after the injunction was granted Qiagen agreed to a consent judgment and the case ended. Prelim. Resp. 2, 17–18; Paper 17, 4.

In other, earlier-filed district court proceedings in Delaware, IBS sued Patent Owner for infringement of five DNA sequencing-by-synthesis related patents, and Patent Owner responded by asserting the ’537 patent (and two other patents) against IBS. Pet. 5. *The Trustees of Columbia University v. Illumina, Inc.*, 1:12-cv-00376-GMS (D. Del.). This litigation was stayed based on eight requests for *inter partes* review (including IPR2013-00517). Pet. 5. According to Petitioner, although all the challenged claims in seven of the eight IPRs were canceled, “certain claims of the ’537 patent survived.” Pet. 5–6. The Delaware litigation ended via order of dismissal dated August 2, 2017, apparently based on the parties’ “negotiated settlement.” See *The Trustees of Columbia University*, 1:12-cv-00376-GMS (document 132 (Stipulation and Order of Dismissal)).

CGI filed the present petitions for *inter partes* review (IPR2017-02172 and IPR2017-02174) on October 5, 2017. The petition in IPR2017-02172 challenges claims 1, 2, 4–6, and 8 as obvious over Tsien, Greene & Wuts, and Zavgorodny, and challenges claim 3 as obvious over Tsien, Greene & Wuts, Zavgorodny, and Prober.

III. ANALYSIS

A. *Declining Discretionary Non-Institution under 35 U.S.C. § 314(a)*

Institution of *inter partes* review is discretionary. See 35 U.S.C. § 314(a) (authorizing institution of an *inter partes* review under particular circumstances, but not requiring institution under any circumstances); 37 C.F.R. § 42.108(a) (stating “the Board may authorize the review to proceed”) (emphasis added); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (“[T]he PTO is permitted, but never compelled, to institute an IPR proceeding” under § 314(a).).

Patent Owner argues the Board should exercise its discretion under § 314(a) and deny the Petition pursuant to *General Plastic Indus. Co. Ltd. v. Canon Kabushiki Kaisha*, Case IPR2016-01357 (PTAB Sept. 6, 2017) (Paper 19) (precedential) (hereinafter “*General Plastic*”).¹⁴ Prelim. Resp. 19–27.

Patent Owner acknowledges that Petitioner is not and was not a party to any prior petition or litigation challenging the validity of the ’537 patent’s claims. Paper 17, 1–2; see also Paper 14, 1–4. Petitioner asserts that it

¹⁴ Patent Owner did not, in its Preliminary Response, argue for discretionary denial under 35 U.S.C. § 325(d), unlike in IPR2017-02172.

neither cooperated nor coordinated with any earlier challenge to the '537 patent. Paper 14, 4.

Notwithstanding the above, Patent Owner, relying primarily on the prior and unsuccessful challenges to the '537 patent by *different* parties, urges that we should deny the Petition. Paper 17, *passim*. However, we decline to extend *General Plastic* and discretionary denial under § 314(a) to the facts here. *See, e.g., Pfizer, Inc. v. Genentech, Inc.*, IPR2017-01923 slip op. 23–25 (PTAB Apr. 4, 2018) (declining to expand *General Plastic* to a new petitioner advancing new art and arguments).

B. Overview of the Asserted References

i) Dower (Ex. 1504)

Dower is a U.S. patent that issued in 1996. Dower “provides a method and apparatus for sequencing many nucleic acid sequences immobilized at distinct locations on a matrix surface.” Ex. 1504, 1:21–25. Dower describes the use of labeled and blocked 3'-OH deoxynucleotides in a cycle that includes elongating a primer by a single nucleotide, removing the blocking group and label, and repeating the process for subsequent labeled and blocked nucleotides. *Id.* at Abstract, Fig. 8, 4:44–5:2, 15:35–40; *see also* Ex. 1601, ¶ 25. With respect to this DNA sequencing method, Dower further discloses:

DNA polymerase, or a similar polymerase, is used to extend the chains by one base by incubation in the presence of dNTP analogs which function as both chain terminators and fluorescent labels. . . . When each cluster incorporates the proper one of the four bases and the fluorescence scanning is complete, the matrix is stripped of the label and chain terminators are deblocked for a next round of base addition. Because the base addition is directed by the template strand, the complementary sequence of the fragments at each address of the matrix is deduced.

Ex. 1504, 23:15–32.

Dower teaches a detectable label may be attached to the nucleobase or elsewhere on the molecule provided the position is compatible with appropriate polymerization. *Id.* at 15:54–59, Fig. 9. According to Dower, when different structures are used as the detectable label and the chain terminator/blocking group (i.e., the label and blocking group are different moieties and/or are located at different locations on the molecule), it is preferable to simultaneously deprotect the 3'-position and cleave the label using the same conditions. *Id.* at 25:23–40. Dower teaches “[t]he appropriate reaction conditions are those used for conventional sequencing reactions with the respective polymerases” and “[t]he conditions are then modified in the usual ways to obtain the optimal conditions” *Id.* at 17:25–29. Dower further teaches that “[t]he removal reaction will preferably be achieved using mild conditions.” *Id.* at 15:52–54.

Dower identifies useful blocking groups, but does not disclose an azido or azidomethyl group. *Id.* at 10:50–53, 18:16–20, 18:52–63, Fig. 6. Dower also does not teach the use of a linker when the label is attached to the nucleobase. Pet. 26.

ii) Church (Ex. 1606)

Church is an international patent application that published in 2000. Like Dower, it also relates to DNA sequencing-by-synthesis methods. Ex. 1606, Abstract; *id.* at 6:9–25. Church teaches, *inter alia*, the use of a detectable label, such as a fluorophore, that is attached to the base by a cleavable disulfide linker. *Id.* at 17:10–11, Fig. 5. Church also teaches the use of thiol compounds, such as DTT (dithiothreitol) to reduce/cleave the disulfide linkage. *Id.* at 68:12–13. Church does not disclose a reversible blocking group that protects the 3'-OH of a nucleotide's deoxyribose ring.

iii) Zavgorodny (Ex. 1508)

Zavgorodny is a synthetic organic chemistry paper published in 1991, and it relates to the chemical synthesis of nucleosides.¹⁵ Ex. 1508, 7593. Zavgorodny discloses over 100 compounds that are described as “useful specifically blocked synthons.” Ex. 1508, 7595. Zavgorodny does not, however, disclose any specific use for these compounds and, specifically, does not disclose their use in DNA sequencing methods. See Ex. 2023, 104:10–14, 105:23–106:3.

Zavgorodny identifies 21 potential protecting groups for the 2'- and 3'-OH groups of a deoxyribose sugar. Ex. 1508, 7594. One of those groups is an azidomethyl (CH_2N_3). *Id.* Zavgorodny discloses the “[a]zidomethyl group is of special interest, since it can be removed under very specific and mild conditions, viz. with triphenylphosphine in aqueous pyridine at 20 °C.” *Id.* at 7595.

C. *A Person of Ordinary Skill in the Art*

Petitioner proposes the following definition for the person of ordinary skill in the art:

a member of a team of scientists working on the research and development of DNA analysis and sequencing techniques. Such a person would have held a doctoral degree related to bioorganic chemistry, biological chemistry or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience directed toward the research and development of DNA analysis and sequencing technologies.

¹⁵ As described in the '537 patent, a “nucleoside” is similar to a nucleotide but lacks phosphate moieties. Ex. 1501, 4:59–63 (“A ‘nucleoside’ is structurally similar to a nucleotide, but are missing the phosphate moieties.”); see also Ex. 1601, ¶ 158 n.6.

Pet. 13. Petitioner acknowledges (Pet. 14, n. 1) that its proposed definition is substantially similar to Patent Owner’s proposed definition, which reads:

a member of a team of scientists addressing SBS product development. Such a person would have held a doctoral degree in chemistry, molecular biology, or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience. Thus, a person of ordinary skill includes a person having a doctoral degree in a field related to chemistry, and at least five years of laboratory experience directed toward the research and development of DNA sequencing technologies.

Prelim. Resp. 26; *see also* Ex. 1592, 9–10.

We do not, for purposes of this Decision, discern a material difference between the parties’ definitions, which are not inconsistent with the prior art of record. As Petitioner bears the burden, we rely on Petitioner’s definition, but our analysis would be the same under either proposal. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required where the prior art itself reflects an appropriate level and a need for testimony is not shown) (internal quotation marks and citation omitted).

D. Claim Construction

In an *inter partes* review, we interpret claim terms in an unexpired patent based on the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming the broadest reasonable construction standard in *inter partes* review proceedings). Under that standard, we presume a claim term carries its “ordinary and customary meaning,” which “is the meaning the term would have to a person of ordinary skill in the art in question” at the time of the

invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). We need only construe terms in controversy, and only to the extent necessary to resolve that controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

The Board previously interpreted claim 1 of the '537 patent in IPR2013-00517, and the Petitioner contends that interpretation should control here. Pet. 23. Patent Owner also cites the Board's previous interpretation, and asserts that "[n]o additional claim construction is required at this stage." Prelim. Resp. 27.

We adopt the Board's prior construction of claim 1. As previously stated by the Board, claim 1 is construed "as encompassing the use of any protecting group attached via the 2' or 3' oxygen atom of a [sugar] moiety, in which the protecting group can be modified or removed to expose a 3' OH group." Ex. 1594, 6. Claim 1 further expressly requires "the protecting group comprises an azido group." Ex. 1501, 19:58–59. Petitioner also urges that claim 1 must be construed so that it "does not require removal of the protecting group to allow subsequent nucleotide incorporation" or "quantitative removal." Pet. 23 (citing *Intelligent Bio-Systems*, 821 F.3d at 1364, 1367). We agree the claim 1 does not recite such removal, and we do not depart from the Board's and Federal Circuit's statements on the matter. *Intelligent Bio-Systems*, 821 F.3d at 1367; Ex. 1594, 7.

E. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious to the person of ordinary skill in the art at the time of the invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis

of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

Importantly, “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. “[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does.” *Id.* Indeed, even “[i]f all elements of a claim are found in the prior art, . . . the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success.” *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015). “[P]redictability is a touchstone of obviousness” and “the ‘predictable result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (citations omitted).

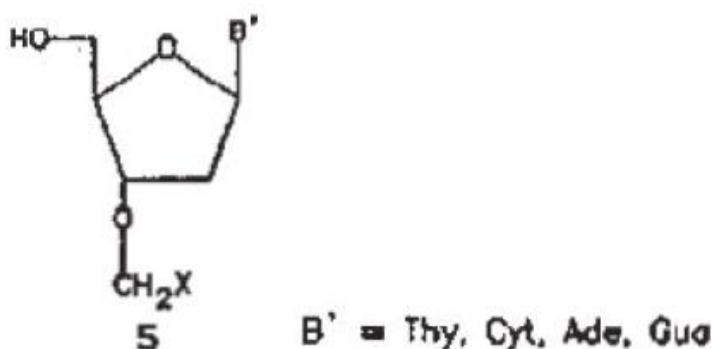
F. Ground 1: Obviousness over Dower, Church, Zavgorodny

Petitioner asserts that claims 1, 2, 4–6, and 8 would have been obvious over the combined teachings of Dower, Church, and Zavgorodny. Pet. 25. According to Petitioner, “Dower . . . describes SBS in much the same way as the ’537 patent.” *Id.* Among other things, Petitioner points to Dower’s teaching of “nucleotides that ‘have a removable blocking moiety to

prevent further elongation’ and that ‘both a blocking moiety and labeling moiety will be often used.’” *Id.* (quoting Ex. 1504, 4:65–5:2). Petitioner further cites to Dower’s teaching that the “fluorophore and 3’ blocking group are removed by the same treatment in a single step (preferably)” Ex. 1504, 25:23–40; Pet. 25.

According to Petitioner, “the only elements of claims 1–2, 4–6 & 8 that are not described in Dower are the use of an azido or azidomethyl protecting group, which are disclosed in Zavgorodny, and the use of a linker when the label is attached to the base.” Pet. 26. Petitioner cites Church as disclosing that it was known in the art to use a cleavable disulfide linker to attach a fluorophore to a nucleobase. Pet. 27–28 (citing, e.g., Ex. 1606, Fig. 5, 17:10–11).

Petitioner turns to Zavgorodny as teaching an azidomethyl protecting group and the conditions for its removal. Pet. 29–30. Petitioner asserts that “Zavgorodny discloses a 3’-O substituted nucleoside . . . where X can be N₃.” *Id.* at 29. In support, Petitioner identifies a portion of a figure disclosed in Zavgorodny, reproduced below, related to “formula 5.”



Pet. 29–30; Ex. 1508, 7594. This figure relates to a pathway for the chemical synthesis of nucleosides and, in the portion shown above, depicts the structure of a substituted nucleoside, where B' represents a nucleobase

(T, C, A, or G), and the 3' oxygen atom of the sugar moiety is attached to CH₂X. *Id.* As described in Zavgorodny, “X” may be a hydrogen (H), a fluorine (F), an azide (N₃), or a variety of other chemical groups. *Id.*

Petitioner asserts that, “[w]hen X is N₃, the 3'-OH of the sugar moiety is protected by azidomethyl, –CH₂N₃, as recited in [dependent] claim 6.” Pet. 30. Petitioner cites Zavgorodny’s disclosure that an “[a]zidomethyl group is of special interest, since it can be removed under very specific and mild conditions, *viz.* with triphenylphosphine in aqueous pyridine at 20°C.” Ex. 1508, 7595; Pet. 30. Petitioner contends “[t]his protecting group was also disclosed in other prior art, including Young,^[16] Loubinoux, Greene & Wuts, and Zavgorodny 2000.^[17]” Pet. 30.

In selecting a suitable protecting group for use in a DNA sequencing-by-synthesis (SBS) method, Petitioner contends the ordinarily skilled person would have focused on “three primary issues.” Pet. 20. Those issues, according to Petitioner, are: “(1) the ability of a polymerase to incorporate the modified nucleotide with the protecting group, (2) the selection of deblocking conditions that do not harm the DNA, and (3) the incorporation and deblocking steps that result in a yield that is reasonable for the

¹⁶ Travis Young, *A Strategy for the Synthesis of Sulfated Peptides*, A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry) at the University of Wisconsin-Madison (2001). Exs. 1549 and 1551. Petitioner submits declarations in support of the prior art status of Young. Exs. 1548, 1550, 1552. Patent Owner does not in its Preliminary Response dispute that Young is prior art.

¹⁷ S.G. Zavgorodny et al., *S,X-Acetals In Nucleoside Chemistry. III. Synthesis of 2'- and 3'-O-Azidomethyl Derivatives of Ribonucleosides*, 19 NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS 1977–91 (2000). Ex. 1509.

desired application.” *Id.* (citing Ex. 1601 ¶ 127); *see also id.* 38–39 (citing Ex. 1504, 18:11–16). Petitioner further alleges the skilled person is capable of optimizing SBS processes (e.g., optimizing reaction conditions), and would appreciate many potential uses for modified nucleotides (e.g., sequencing methods requiring fewer cycles). *Id.* at 21–23.

Against this asserted background, Petitioner argues all the limitations are taught in the prior art, and that it would have been obvious to combine the relevant teachings of Church and Zavgorodny with Dower’s sequencing methods to arrive at the subject matter recited in claim 1. Pet. 32–34. First, Petitioner contends the ordinary artisan would “have been motivated to use Church’s disulfide linker because they would have expected to achieve efficient cleavage using mild conditions.” *Id.* at 33. Second, Petitioner contends it would have been obvious to add “Zavgorodny’s azidomethyl protecting group because (1) it would have been ‘a simple substitution of one known element for another to obtain predictable results’ and (2) a POSITA would have been motivated to use azidomethyl because of its advantageous properties and its ability to be simultaneously cleaved with Church’s disulfide linker.” Pet. 34 (citing Ex. 1601 ¶¶ 128, 180–83).

Patent Owner does not, in its Preliminary Response, dispute Petitioner’s contention that it would have been obvious to use Church’s disulfide linker in Dower’s methods.¹⁸ Instead, Patent Owner argues the ordinarily skilled person would not have been motivated to use Zavgorodny’s azidomethyl group in a DNA sequencing method like disclosed in Dower. Prelim. Resp. 27–50. Patent Owner contends, among

¹⁸ Patent Owner supports the arguments in its Preliminary Response with, among other evidence, a Declaration of Floyd Romesberg, Ph.D. (Ex. 2024).

other things, that the rigid shape and steric bulk of an azidomethyl group would have discouraged the skilled person from using that group as a 3'-OH protecting group for DNA sequencing, where a polymerase must accurately and efficiently incorporate the labeled and blocked nucleotide into the nucleic acid molecule. *Id.* at 29–39.¹⁹ Patent Owner also contends that Zavgorodny's deblocking conditions would not be "mild" for DNA sequencing and, quite the opposite, would have been thought to harm (e.g., denature) DNA. *Id.* at 40–45. According to Patent Owner, the Petition fails to adequately address the evidence of DNA denaturation under these and other conditions. *Id.* Patent Owner also argues the ordinary artisan would have been discouraged from using an azidomethyl group in Dower's methods because of expected inefficient cleavage/deblocking of that group. *Id.* at 45–47. As to Petitioner's "simple substitution" theory, Patent Owner contends, *inter alia*, that this theory is undermined by Petitioner's own evidence, which confirms that much more than just exchanging a protecting group is involved and that myriad other technical decisions would be required, which together make the results unpredictable. *Id.* at 51–52.

i) "Simple Substitution"

Turning to Petitioner's first proffered rationale, we find that, at the time of the invention, the effective use of an azidomethyl moiety as a 3' protecting group in Dower's sequencing methods would not have been regarded as a simple or straightforward substitution. Indeed, evidence of record suggests the opposite, which we explain further below.

¹⁹ Patent Owner further argues that Petitioner has not shown a "reasonable expectation of success" in arriving at the "incorporating" step of claim 1. Prelim. Resp. 39–40.

As a preliminary matter, as Patent Owner notes, in the several years leading up to Patent Owner's invention, over ten research teams had sought to identify 3'-protecting groups that were effective for DNA sequencing like disclosed in Dower. Prelim. Resp. 8–10, 50–51. *See, e.g.*, Ex. 1504 (Dower) (disclosing acetyl, tBOC, etc.); Ex. 1541 (Metzker) (investigating 3'-O-methyl, 3'-O-acetyl, and 3'-O-allyl, among several others); Ex. 1503 (Tsien) (investigating 3'-O-allyl and other groups); Ex. 1538 (Ju) (investigating 3'-O-allyl and 3'-O-methoxymethyl groups). None, however, before Patent Owner appear to have identified or suggested an azido group as suitable for that purpose.

Petitioner alleges that an azidomethyl moiety was a known protecting group. Pet. 35–36. But Petitioner has not shown sufficiently that all such protecting groups are simply interchangeable regardless of the group that is being protected or the use to which the protected molecule is to be put. Greene & Wuts, for example, includes an entire chapter devoted to suitable protecting groups for phenols and an azidomethyl group (“azidomethyl ether”) is mentioned in that chapter. Ex. 1505, 260. Greene & Wuts devotes an entirely different chapter to suitable protecting groups for aliphatic alcohols, which include the relevant types of hydroxyl groups that appear in nucleotides. Ex. 1505, 17. Tellingly, an azido group is not mentioned in the chapter on suitable protecting groups for aliphatic alcohols. Petitioner's expert acknowledges that Greene & Wuts is widely used and cited among skilled persons screening potential protecting groups for various functional groups (and thus, we consider it to be reasonably authoritative on the

topic).²⁰ Ex. 1601, ¶ 35. Petitioner's expert opines that a skilled person "would not feel restricted" by the way Greene & Wuts categorizes the protecting groups and would have looked to both chapters. *Id.* ¶ 36. We are not, however, persuaded. Although Greene & Wuts indicates that "[m]any of the protective groups developed for alcohol protection are also applicable to phenol protection" and "thus, the chapter on alcohol protection should also be consulted" (Ex. 1505, 248), Petitioner directs us to no reciprocal disclosure suggesting the phenol chapter should be consulted for suitable protecting groups for aliphatic alcohols. Moreover, because Greene & Wuts teaches that phenols are better leaving groups than simple alcohols, we cannot conclude that a protecting group that works well for a phenol would be expected to work well and be readily removed in good yield for aliphatic alcohols. Ex. 1505, 248 ("Ethers are the most widely used protective groups for phenols, and in general, they are more easily cleaved than the analogous ethers of simple alcohols."). This evidence cuts against Petitioner's simple substitution theory.

Petitioner cites Zavgorodny's disclosure in 1991 of a 3'-O-azidomethyl substituted deoxyribose sugar moiety, which Petitioner

²⁰ Greene & Wuts discloses several desired properties when selecting protecting groups. Ex. 1505, 1. For example, Greene & Wuts discloses "[t]he protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group . . . [and] should have a minimum of additional functionality to avoid further sites of reaction." *Id.* Greene & Wuts further suggests that the organic synthesis of molecules using protecting groups is far from predictable. *Id.* ("[T]he science and art of organic synthesis, contrary to the opinions of some, has a long way to go before we can call it a finished and well-defined discipline, as is amply illustrated by extensive use of protective groups during the synthesis of multifunctional molecules.").

contends is “precisely the same chemical group and location as it is claimed to protect in the ’537 patent.” Pet. 36. Yet Zavgorodny suggests no specific use for its substituted molecules. *See* Ex. 2023, 104:10–14, 105:23–106:3. Neither does Zavgorodny disclose whether the azidomethyl group is removable at any particular efficiency, much less an efficiency suitable for DNA sequencing methods. *See, e.g.*, Ex. 1503, 16:21–30, 20:33–34; Ex. 1538, 21:11–13.²¹ And, on this record, Patent Owner has cited evidence that the conditions Zavgorodny teaches are “very specific” to removing an azidomethyl group would risk denaturing DNA, and therefore would not be considered mild for DNA sequencing methods. Ex. 1508, 7595; Prelim. Resp. 44; Ex. 1533, 57–58 (describing pyridine as an “especially effective” DNA denaturant); *see also* Ex. 1536, 171 (disclosing pyridine as among “the most effective [DNA] denaturants examined.”).

Petitioner also cites Young’s teaching in approximately 2001 of using an azido protecting group. Pet. 35; Ex. 1551. Young relates to synthesis of sulfated peptides and, more specifically, synthesis of “a novel protected tyrosine derivative.” Ex. 1551, iii. Young “chose the azidomethylene protecting group for protection of the tyrosine *phenolic* hydroxyl group,” and discovered that “peptide synthesis using this building block proceeds efficiently.” *Id.* (emphasis added). Citing Loubinoux (which also teaches use of an azido group to protect phenols), Young discloses that “[r]eduction of the azide should result in the unmasking of the tyrosine phenol.” *Id.* at

²¹ Although Dower does not expressly recite a strict quantitative deblocking requirement (at or near 100% efficiency) as recited in Tsien for DNA sequencing reactions. Relevant prior art does, however, generally demonstrate that high efficiency deblocking and product yields are desired, if not necessary. Ex. 1503, 16:21–30, 20:33–34; Ex. 1538, 21:11–13.

53; Ex. 1506, 6055. In a chapter called “Future Directions,” Young states that an azidomethylene group could be used to protect hydroxyl groups on serine and threonine. Ex. 1551, 73–74.

Petitioner does not show adequately how Young’s disclosure related to synthesis of sulfated peptides, and deblocking of phenols on tyrosine residues, would have been understood as applicable to DNA sequencing methods. Young, like Loubinoux and Greene & Wuts, describes the use of an azido group to protect phenols. *See* Ex. 1506, 6055; Ex. 1505, 260. And Young’s statement about a possible use of an azidomethylene to protect hydroxyl groups on other amino acid residues, in the context in which it was made, appears to be little more than a hypothesis. Ex. 1551, 73–74. We find, on this record and absent hindsight, that Young does not provide sufficient direction or motivation to use a 3’-OH azidomethyl protecting group in DNA sequencing methods disclosed in Dower. Moreover, as Patent Owner points out, Young’s cleavage conditions (e.g., using trifluoroacetic acid (“TFA”)), even if resulting in high yields for Young, would not be considered mild for DNA sequencing. Prelim. Resp. 44–45; *see, e.g.*, Ex. 2024 ¶ 34 (explaining that aqueous TFA degrades DNA).

Finally, we are unpersuaded that Petitioner’s “simple substitution of one known element for another” theory applies to the relevant protecting group here, where even the evidence proffered by Petitioner suggests that numerous technical decisions and modifications, beyond simply selecting a protecting group, would be required. As Patent Owner asserts, Petitioner’s “own witness undermines and contradicts [Petitioner’s] assertion that an azidomethyl group could be simply substituted into Dower’s methods.” Prelim. Resp. 52. Petitioner’s expert opines that Dower’s sequencing methods depend on many variables beyond picking a protecting group, and

that the skilled person would need to select and endeavor to optimize (in an apparent trial-and-error manner), among other things, reaction conditions, reagents, temperature, pH, concentration, and time. Ex. 1601 ¶¶ 79, 81.

Petitioner does not, however, identify specific reagents or deblocking conditions that are disclosed in Dower that would be suitable for use with an azidomethyl protecting group.²² And, as explained above, Petitioner has not shown adequately that the “very specific” conditions proposed in Zavgorodny would have been considered suitable for DNA sequencing.

ii) “Advantageous Properties”

Petitioner contends the ordinarily skilled person would have been “highly motivated” to use Zavgorodny’s azidomethyl group with the reversibly blocked nucleotides of Dower (as modified by Church) because of azidomethyl’s “advantageous properties.” Pet. 42. Petitioner asserts an azidomethyl protecting group is removable under “mild and specific” conditions. *Id.* at 43. Petitioner asserts the “azidomethyl group of

²² Petitioner asserts that only ordinary skill is required to select appropriate incorporation and deblocking conditions. Pet. 36–38. The art reflects that the level of ordinary skill is high, and even assuming selection of other reactants, conditions, etc. is possible, the Petition does not meet the burden of persuasively identifying the set of conditions, etc. that would have predictably been selected and appropriate for DNA sequencing as in Dower. The conditions that are identified (e.g., Zavgorodny’s “very specific and mild” deprotecting conditions) would, on this record, have been considered unsuitable for use with DNA. Ex. 1508, 7595; Ex. 1533, 57–58. Notably, by describing conditions for removing an azidomethyl protecting group of the substituted nucleoside as “very specific,” Zavgorodny undermines somewhat the notion that the skilled person would simply choose other conditions with predictable results. Ex. 1508, 7595. Even roughly 10 years later, Zavgorodny ’00 does not suggest different removal conditions, but repeats the same, specific removal conditions from 1991. Ex. 1509, 1980.

Zavgorodny . . . could be removed using conditions that would simultaneously cleave the disulfide linker of Church.” *Id.* at 46. Petitioner contends the azidomethyl group is small and could be incorporated by a polymerase in Dower’s SBS methods. *Id.* at 47–48. Petitioner also contends, the skilled person “would not necessarily need to use a protecting group with a very high deblocking efficiency” and, in any case, a “desire for high deblocking efficiency would have been yet another motivating factor for a POSITA considering the use of an azidomethyl protecting group, particularly in light of the teachings of Young and Loubinoux.” *Id.* at 49.

We are not persuaded the alleged “advantageous properties” of Zavgorodny’s azidomethyl protecting group would have prompted the ordinarily skilled person to use it in combination with Dower and Church. We explain further below.

Conditions that are mild in one context are not necessarily mild and otherwise suitable in another. As explained above, the co-solvent pyridine used in Zavgorodny’s allegedly “mild” conditions was a known DNA denaturant. Ex. 1533, 57–58; Ex. 1536, 171. Petitioner admits, however, that “mild conditions” suitable for use in Dower’s methods “are those that would not ‘degrade the DNA template moiety.’” Pet. 20–21. Petitioner has not, thus, adequately shown that a skilled person would have been motivated to use Zavgorodny’s azido-protecting group and deblocking conditions.

Petitioner also fails to show sufficiently that other disclosed azidomethyl deblocking conditions would have been thought of as mild and appropriate for the DNA sequencing methods of Dower at the time of the invention. At the outset, it is unclear if Petitioner is actually proposing to further modify the method based on the combination of Dower, Church, or Zavgorodny with specific conditions recited in Young or Loubinoux. If

Petitioner is making such a proposal, it fails to do so clearly and persuasively. Young, for example, relates to deprotection of phenols (not aliphatic alcohols) and there is no showing that its deprotection conditions would work effectively with DNA. To the contrary, Young's strongly acidic, 95% aqueous TFA solution, would have been considered harmful to DNA. See, e.g., Ex. 2024, ¶ 34; Ex. 2026, 4997 ("Dupurination is accelerated at low pH and high temperature."). Loubinoux also relates to removal of an azido moiety from phenols, and teaches two sets of reaction conditions: one involving a triphenylphosphine followed by water and tetrahydrofuran, and another involving treatment with hydrogen in the presence of palladium on carbon. Ex. 1506, 6057. Yet the Petition does not persuasively show that Loubinoux's conditions are appropriate for deblocking of an azidomethyl group in DNA sequencing methods. Insofar as Loubinoux's triphenylphosphine treatment is concerned, Loubinoux teaches this method was less effective than the hydrogen treatment, which at best resulted in product yields of 60–80%. *Id.*²³ We thus agree with Patent Owner, on this record, that "Loubinoux would have led the ordinary artisan to believe that phosphine-based cleavage was the least desirable of the disclosed cleavage methods," discouraging the skilled artisan from pursuing it. Prelim. Resp. 46. And, even as to this less effective treatment, Patent Owner provides evidence that phosphine deblocking conditions produce amines that can harm DNA molecules. Prelim. Resp. 41–43 (citing Ex.

²³ As we explained above, Greene & Wuts evidences that phenols are more easily cleaved than simple alcohols. Ex. 1505, 248. Accordingly, to the extent predictable, aliphatic alcohols would be expected to be cleaved at lower efficiencies than phenols. *Intelligent Bio-Systems*, 821 F.3d at 1368–69; *Illumina*, 207 F.Supp.3d at 1090.

1546, 85:10–13); *see also* Ex. 1534, 2840 (describing THF as a DNA denaturant); Ex. 1598, ¶ 55.

Moving to the next alleged “advantageous” property, Petitioner contends “a POSITA would have known that phosphines, like those used to deprotect the azidomethyl group, would also cleave Church’s disulfide linker.” Pet. 46. Thus, in order to simultaneously remove an azidomethyl group and cleave the disulfide linker of Church, Petitioner proposes it would have been obvious to use TCEP (tris(2-carboxyethyl)-phosphine) as the reducing agent. *Id.* Patent Owner, however, presents argument and evidence to the contrary. Citing Stanton, Patent Owner argues “the amine group formed by the reaction of a phosphine with an azido group would cleave the phosphate ester backbone of DNA.” Prelim. Resp. 43. More specifically, Stanton teaches:

The amino group may be generated in situ from the corresponding azido sugar by treatment with tris(2-carboxyethyl)-phosphine (TCEP) after the azide-modified polynucleotide has been formed. *The amino group, once formed, spontaneously attacks the phosphate ester linkage resulting in cleavage.*

Ex. 1546, 85:10–13 (emphasis added). Patent Owner contends it raised Stanton’s disclosures about DNA degradation when TCEP is used in the prior IPR (IPR2013-00517), yet the Petition fails to address this evidence. Prelim. Resp. 43 (citing Ex. 2031 ¶ 5). On this record, we are persuaded this evidence is yet another factor that would have discouraged the ordinarily skilled person from pursuing the modification of the prior art proposed by Petitioner, including the use of TCEP as an azidomethyl reducing agent in DNA sequencing methods as proposed.

Petitioner next urges that the small size of an azidomethyl group would have suggested its use in Dower's SBS methods. Pet. 47. According to Petitioner, "DNA polymerase leads it to discriminate against the incorporation of nucleotide analogues bearing a large 3'-OH protecting group." *Id.* Further, Petitioner contends "a POSITA would have expected azidomethyl to be inert to the polymerase" and otherwise biocompatible, as allegedly "bolstered by prior art demonstrating that azides were unreactive toward polymerases." *Id.* at 48. Petitioner cites evidence, *inter alia*, relating to the incorporation by polymerase enzymes of the compound 3'-azido-3'-deoxythymidine (or "AZT"), which is an antiviral DNA chain-terminating compound often used to treat HIV. Ex. 1601, ¶¶ 118, 144; Ex. 1515, 21459. In this compound, the azido group (N₃) is attached directly to the 3'-carbon of the deoxyribose moiety. Ex. 2024, ¶ 28.

Petitioner has not shown that the ordinarily skilled person would have predictably turned to an azidomethyl group based on its allegedly small size. Rather, as Patent Owner points out, the azido group itself is relatively inflexible and provides significant steric bulk at the polymerase active site. Prelim. Resp. 32 (describing the size and shape of the three azido nitrogen atoms); Ex. 2024, ¶¶ 24–26 (same). Although Petitioner cites to AZT incorporation, Patent Owner counters with evidence that "AZT incorporation essentially overstuffs the polymerase active site with steric bulk of the linear and rigid 3'-azido [N₃] group." *Id.* at 37; Ex. 2024 ¶¶ 25–30. More specifically, Patent Owner cites Boyer's study in 2001, finding:

when AZT is incorporated, the AZT interferes with the formation of the closed ternary complex [of the polymerase]. We believe that the problem is steric and that the large azido group interferes with either the ability of AZT to occupy the P [portion of the

active] site, or the ability of the incoming dNTP to enter the N [portion of the active] site, or both.

Ex. 2030, 4833; Prelim. Resp. 36–37. Thus, while some polymerases might incorporate AZT, the size and steric bulk of the N₃ moiety alone is described as fully occupying the enzyme active site. Ex. 2024, ¶ 29. Petitioner does not explain adequately why, at the time of the invention, the *larger* azidomethyl moiety (which includes, in addition to the three linear nitrogen atoms, an extra oxygen, carbon, and two hydrogen atoms) would have been expected to fit within the active site. Prelim. Resp. 37; Ex. 2024, ¶¶ 28–30. The allegedly small size of an azidomethyl moiety does not, alone, answer this question. As Patent Owner’s expert Dr. Romesberg explains, a small size is not predictive of incorporation: “Metzker demonstrated that a nucleotide analog with a small 3’-O-acyl group was not incorporated, while that with a small 3’-O-allyl group was incorporated.” Ex. 2024, ¶ 31 (citing Ex. 1541 (Metzker), 4263, 4265).²⁴ Accordingly, Dr. Romesberg testifies that “[t]he rigid steric bulk of the 3’-O-azidomethyl group would have discouraged a person of ordinary skill in the art from using [that] group as a substrate to be incorporated by a polymerase.” Ex. 2024, ¶ 31.

Petitioner contends an azidomethyl group can adopt “rotameric states” that could reduce its steric bulk so the ordinarily skilled person would have expected minimal steric interference, but Petitioner fails to support this

²⁴ See also Ex. 2024, ¶ 30 (citing Ex. 1526, 1619 (explaining a significant steric gate in RNA (which includes only an OH instead of an H at the 2' ribose position) compared to DNA, and disclosing that dNTPs are preferred over rNTPs by over 10,000 fold by the wild-type enzyme. Hence, the presence of an additional oxygen atom near the 3' site can have significant consequences relative to incorporation of nucleotides by a polymerase.

assertion with sufficiently persuasive evidence. Pet. 47. The evidence cited by Petitioner shows, compared to azidomethyl, substantially non-polar blocking moieties with longer and flexible arms designed to keep the bulkier groups away from the catalytic center of the polymerase. See Ex. 1527, 212–13; Prelim. Resp. 33–34 (annotated drawings from Metzker); Ex. 2024, ¶¶ 24–27 (“The linear and rigid shape of an azido group is expected to behave very differently than the flexible and adaptable 3’-moieties that Hovinen and Metzker reported were incorporated”). We are, thus, not persuaded the structures cited by Petitioner would have been predictive of the behavior of a 3’-azidomethyl substitution at the active site. This is another reason why the Petition does not show a sufficient motivation to use an azido-protecting group in Dower’s methods at the time of invention.

Moving to the final alleged “advantageous” property related to deblocking efficiency (Pet. 48–51), the Petition remains deficient. As explained above, concerns about the rigidity and steric bulk of an azidomethyl group, and DNA-harmful deblocking conditions proposed to remove it would have discouraged its use. The ordinary artisan, based on these considerations, was more likely to expect, at best, inefficient incorporation and deblocking when used for DNA sequencing as described in Dower. In using an azidomethyl protecting group in this way, the skilled person would not be exploiting an *advantage* of an azidomethyl group, but an expected *disadvantage*. We are not persuaded, absent hindsight, that the ordinarily skilled person would have done so — even in DNA sequencing applications with shorter-read lengths and where high efficiency deblocking is allegedly not as critical. Pet. 48–49.

As to whether the ordinary artisan would have expected “high efficiency deblocking” based on Young and Loubinoux (Pet. 49–51), that

too is doubtful. The efficient removal reported in Young related to deprotection of phenols, which, as described elsewhere in the art, are more easily cleaved than the hydroxyl groups of simple alcohols. Ex. 1551, 53; Ex. 1505, 248. Young also does not disclose deblocking conditions suitable for DNA or describe deblocking of an azidomethyl moiety to reveal a 3'-OH on substituted nucleotide, much less high efficiency removal in that context. Ex. 2024, ¶ 34. So too, Petitioner has not shown adequately that Loubinoux's cleavage methods would have been suitable for use with DNA or would have suggested "the azidomethyl group could be deblocked in extremely high efficiency" when used in Dower's methods as Petitioner contends. Pet. 50. As Patent Owner highlights, Loubinoux's methods would have been expected to degrade DNA. Prelim. Resp. 46; *see also e.g.*, Ex. 1598, ¶¶ 44–47; Ex. 1546, 85:10–13; Ex. 1534, 2840. Loubinoux, as with Young, also related to deblocking of the more easily cleaved phenols, not aliphatic alcohols like the relevant 3'-O-substituted nucleotides here. Ex. 1504, 6055, 6057; Ex. 1505, 248.²⁵ Even if Loubinoux (or Young) reported "high efficiency deblocking" as alleged, Petitioner fails to make a sufficient evidentiary showing that efficiencies expected or observed with deblocking of phenols would have been expected with deblocking of an azidomethyl protecting group from the relevant nucleotides here. We thus remain unpersuaded the ordinarily skilled person would have been motivated to use an azido-protecting group in Dower's DNA sequencing methods.

²⁵ The Board and Federal Circuit earlier considered the relevant teachings of Loubinoux cited here and concluded Loubinoux, particularly when considered with Greene & Wuts, would have suggested the azidomethyl protecting group would have been expected to be inefficiently cleaved to expose a 3'-OH of a nucleic acid molecule. *See supra* Section II.E.ii-iii.

For the above reasons, we are not persuaded the record before us establishes a reasonable likelihood that Petitioner will prevail in showing that the subject matter of claims 1, 2, 4–6, and 8 would have been obvious over the combination of Dower, Church, and Zavgorodny. We decline to further address the contentions about Patent Owner’s evidence of secondary considerations of nonobviousness. Pet. 58–62; Prelim. Resp. 55–60.

G. Ground 2: Obviousness over Dower, Church, Zavgorodny, Prober

Petitioner relies on Prober for teaching the additional limitation in dependent claim 3, “wherein the base is a deazapurine.” Pet. 55. Because Ground 2 relies on the combination of Dower, Church, and Zavgorodny (Ground 1), and because we determine that the Petition has not established a reasonable likelihood that claim 1, from which claim 3 depends, would have been obvious over those references as explained above, we similarly determine that Ground 2 is deficient. Petitioner does not assert or show that Prober makes up for the shortcomings discussed above related to the Dower, Church, and Zavgorodny combination and, accordingly, the Petition has not established a reasonable likelihood that claim 3 would have been obvious over Dower, Church, Zavgorodny, and Prober.

IV. CONCLUSION

For the foregoing reasons, we determine Petitioner has not established a reasonable likelihood of prevailing on its assertions that claims 1–6 and 8 of the ’537 patent are unpatentable.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and that we do not institute *inter partes* review of any claim of the '537 patent based on the grounds asserted in this Petition.

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